A novel synthesis of 2,2'-bisindole and its application for the synthesis of indole[2,3-a]carbazole derivatives

A NOVEL SYNTHESIS OF 2,2'-BISINDOLE AND ITS APPLICATION FOR THE SYNTHESIS OF INDOLO[2,3-*a*]CARBAZOLE DERIVATIVES[1]

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Abstract —— A novel oxidative coupling method of 2-lithio-1-methoxyindole was developed resulting in the formation of 2,2'-bis(1-methoxyindole) (**6**). Catalytic hydrogenation of **6** produced 2,2'-bisindole (**9**). Diels-Alder reaction of **9** with dienophiles afforded indolo-[2,3-*a*]carbazole derivatives.

Rebeccamycin (**1**),[2a] staurosporin,[2b] BE-13793C (**2**),[2c] tjipanazoles,[2d] and 6-cyano-5-methoxy-12-methylindolo[2,3-*a*]carbazole[2e] are interesting antibiotics,[2f] having indolo[2,3-*a*]carbazole[2g] as a common skeleton. Their multimodality of biological action such as potent antitumor activity and/or inhibition of protein kinase C or topoisomerase, and so on[2] have attracted much attention on their synthesis.[2] In this communication, we report a simple synthetic method of 2,2'-bisindole[3] and its application for the synthesis of indolo[2,3-*a*]carbazole derivatives in only four steps from 2,3-dihydroindole (**3**).

I. Preparation of 2,2'-bis(1-methoxyindole) and 2,2'-bisindole

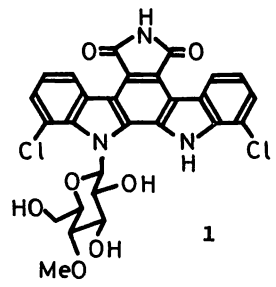
In the previous paper,[4] we have reported that 1-methoxyindole (**4**) is a versatile synthetic building block due to its ready availability[5] from **3** and regioselective formation of 2-lithio-1-methoxyindole (**5**, Figure 1).

Table I. Preparation of 2,2'-Bis(1-methoxyindole) (**6**) from 1-Methoxyindole (**4**)

Run	$CuSO_4$* (mol eq.)	Reaction Conditions Additives	Time (h)	Yield (%) of **6**	Recovery
1	1	—	1	13	52
2	1	O_2	1	27	44
3	3	O_2	1	8	61
4	0.5	O_2	1	29	42
5	1	O_2 and ultra sound	1	34	20
6	0.22	〃	0.5	42	24
7	0.5	〃	1	54	8

* Used after drying $CuSO_4 \cdot 5H_2O$ *in vacuo* at 280°C for 1 h.

Figure 1



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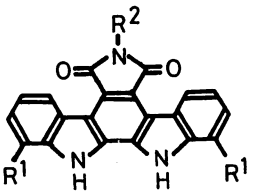
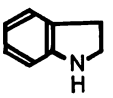


	R^1	R^2
2	OH	H
10	H	Ph



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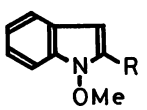
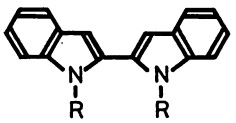
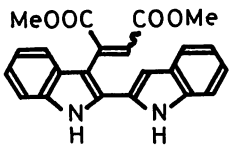


	R
4	H
5	Li
7	Cl
8	CN



	R
6	OMe
9	H



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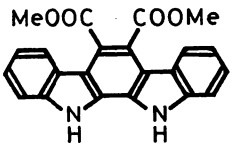

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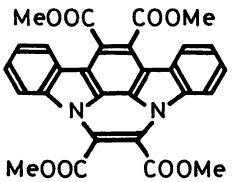

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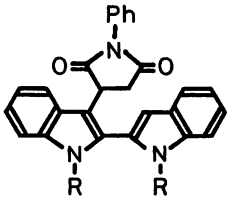

	R
14	OMe
15	H

Now, we wish to report a new oxidative coupling reaction of **5** with anhydrous cupric sulfate ($CuSO_4$). Thus, *n*-butyllithium (1 mol eq.) was added to **4** (1.714 g) in anhydrous tetrahydrofuran under argon atmosphere at -18 °C (ice-NaCl cooling bath). Treatment of the resultant yellow solution of **5** with anhydrous $CuSO_4$ under oxygen atmosphere with ultra-sound stirring at 0°C produced 2,2'-bis(1-methoxyindole) (**6**, 919 mg, 54%), and the results are summarized in Table I. As can be seen from the Table, the presence of oxygen (compare run 2 with 1) and ultra-sound (run 5 with 2) were essential for improving the yield of **6**. Quantity of $CuSO_4$ had a significant effect on the coupling yield, and 0.5 mol eq. was found to be recommendable (runs 4 and 7). Finally, we could obtain **6** in 54% yield, in addition to **4**, with an excellent reproducibility under the reaction conditions of run 7. Although cupric chloride[6] and cuprous cyanide were examined as a coupling reagent under various reaction conditions, the yield of **6** was poorer (6~38%) than that with anhydrous $CuSO_4$, and a significant amount of either 2-chloro- (**7**, 4~21%) or 2-cyano-1-methoxyindole (**8**, 3~10%) was produced as a by-product, respectively.

Catalytic hydrogenation of **6** with 10% Pd/C under atmospheric hydrogen at room temperature for 6 h afforded 2,2'-bisindole[3] (**9**) in 79% yield.

II. Preparation of indolo[2,3-*a*]carbazole derivatives

With suitable building block **9** in hand, we next examined its Diels-Alder reaction.[2g] Treatment of **9** with *N*-phenylmaleimide in *o*-dichlorobenzene at reflux afforded 17% yield of 6-phenylindolo[2,3-*a*]pyrrolo[3,4-*c*]carbazole-5,7(6*H*)-dione (**10**). In the same reaction using a catalytic amount of 10% Pd/C, the yield of **10** was improved to 30%. The reaction of **9** with dimethyl acetylenedicarboxylate in the presence of 10% Pd/C in xylene at reflux produced **11** and **12** in 37 and 9% yields, respectively, while the reaction in *o*-dichlorobenzene at reflux afforded **12** in 36% yield in addition to 17% yield of unknown 2:1 adduct (**13**, deduced based on spectral data). Treatment of **12** with aniline at reflux for 18 h afforded **10** in 48% yield to-

gether with 49% yield of recovery.

On the other hand, the reaction of **6** with *N*-phenylmaleimide in the presence of boron trifluoride etherate at room temperature afforded 68% yield of Michael adduct (**14**). Subsequent treatment of **14** with 10% Pd/C in xylene at reflux produced **10** and 1,1'-demethoxy Michael adduct (**15**) in 32% and 14 % yields, respectively. Treatment of **15** with 10% Pd/C in xylene at reflux also afforded **10** in 42% yield.

Although optimum reaction conditions are not made, we could develop a simple four step synthetic method of indolo[2,3-*a*]carbazole derivatives from **3**. Application of the newly found coupling reaction with $CuSO_4$ to various organometallics, and Diels-Alder reaction of **6** and **9** with dienophiles are currently in progress.

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